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REMARKS/ARGUMENTS

Remarks

Inventorship adjustment:

On October 6, 2003 Applicants submitted a Petition under 37 CFR §1.48(b) to remove Toshiomi Yoshida as an inventor in this application. This Petition was acknowledged as received by the USPTO on October 8, 2003 (copy of post card and Petition are enclosed). As of this date Applicants have not received acknowledgement that the Petition has been granted and that the removal of that inventor was entered of record. Applicants respectfully request that the Examiner respond to this request for the status of this Petition.

Change of Address for Correspondence:

On September 25, 2003, as well as in Applicants' Response mailed September 29, 2003, Applicants requested that all correspondence be addressed to the undersigned at The Dow Chemical Company. The current Office Action mailed December 22, 2003 was still sent to the incorrect address and addressee. This error has cost the Applicants time to prepare their response to this Action because of an untimely received notice of this Office Action from the former owner. Applicants respectfully request that all future correspondence be sent to the address previously given to the Office.

Power of Attorney:

Because the assignment of the present application to The Dow Chemical Company has been recorded on November 18, 2002 at reel/frame 013509/0382, Applicants do not believe that any Power of Attorney is required to be filed in order for the undersigned in-house counsel to prosecute this application under 37 CFR §1.34(a). However, for ease of possible future correspondence and prosecution matters, the Assignee is providing herewith a Power of Attorney, using the Customer Number method that is now permitted.

An Information Disclosure Statement (IDS):

An IDS is provided to include the prior art cited in equivalent applications. Although the present application is a National Phase application from the PCT, the art cited by the PCT in its Search Report and Written Opinion is also included on the IDS as a precaution if the Examiner's files are incomplete.

Election/Restrictions (Responsive to Items 1-3 of the Action):

Applicants note that in the present Action the Examiner has rejoined Groups I and III with Group II from the prior restriction requirement so that the present application now contains claims 1-12 as pending. Claims 13 and 14 are now cancelled in the above claim listing and a divisional application filed separately directed to that nonelected subject matter in accord with 37 CFR §1.144.

Abstract (Responsive to Item 4 of the Action):

The requested Abstract for this application is provided on a separate page as an amendment to the specification above. Because no separate prior Abstract was present in this application, there is no mark-up provided. Additionally, this Abstract is modified from the abstract in the corresponding PCT from which this US application is the National Phase.

Specification – Incorporation by Reference (responsive to Item 5 of the Action):

The specification has been amended as shown above to eliminate the incorporation by reference to a foreign application. Thus no affidavit or declaration is required under the cited case decisions.

Specification – Cross Reference to Related Applications (Responsive to Item 6 of the Action):

The paragraph on page 1, after the title, has been amended as shown above to comply with the objection in Item 6 of the present Action.

Support for the Currently Amended and New Claims:

Claims 1 and 3 have been amended to include mammalian-type sugar chains and is supported at page 6, line 7. The other amendments in claim 1 are for clarity.

Claim 2 has been amended for clarity.

Claim 6 has a typographical error corrected.

Claims 7 and 12 have added explanation of fucose and xylose inserted which is supported at page 12, lines 14-18. The added wording "wherein the glycoprotein produced has no fucose or xylose linked to one or more of the core sugar chain, the outer sugar chain and the terminal sugar chain" results in a lowered fucose or xylose content which is supported by the data, Figure 20 and the Affidavits.

Claims 8-11 are discussed below.

Claim 15 has support as follows: the glycosyl transferase is supported at page 15, lines 3-4; the exogenous glycoprotein is supported at page 15, lines 24-27; the sugar chain is supported at page 6, lines 19-24; and the fucose and xylose is supported at page 12, lines 14-18.

Claims 16 and 17 are supported from page 2, line 18 through page 3, line 30 and claims 9 and 10.

Claim 18 is supported at page 15, lines 27-30.

Claim 19 is supported from page 15, line 30 through page 16, line 3.

Claim 20 is supported at page 16, lines 3-4.

Claim 21 is supported at page 13, lines 2-4.

Claim 23 is expanded to include mammalian-type sugar chains and is supported at page 6, line 7.

Claim 24 is directed to human-type sugar chains and is supported throughout the application including at page 6, line 7.

Applicants believe that all of the above mentioned remarks can be entered where requested and are fully responsive to Items 1-6 of the present Action. If any of these amendments or submissions (such as the IDS) requires a fee, Assignee

authorizes that its Deposit Account No. 04-1512 be charged. None of the above amendments made under these Remarks have been made to overcome any prior art whether cited by this Action or not.

Arguments

Rejection Under 35 USC §101

Claims 8 and 11

These comments are responsive to Items 7 and 8 of the Action.

Claims 8 and 11 are now amended as shown above to more clearly be directed to a transgenic plant cell and transgenic plant, respectively. These plants are genetically engineered and have specific requirements to regenerate, use media and additives to facilitate their growth, and require human know-how to maximize such possible use. The hand of man is clearly required. Also it is highly unlikely these plants would develop or exist without human intervention and continued assistance. The term “transformed” appearing at page 17, lines 2-5, 25 and 33 and numerous other locations in the specification, clearly supports these amendments to the claims. The amendments to claims 9 and 10 also use this same specification support for similar amendments.

For all glycosyltransferases within the above amended claims 1-24, these inserted enzymes must be active in a plant cell, but without having a detrimental effect on the plant cell or on the transgenic plant as a whole. A plant does not possess naturally the enzymes required to do the needed glycosylation so that they must be inserted to achieve the desired result. Also any enzymes engineered into the plant must, in order to be functional, be inserted into the membrane of the plant Golgi at the appropriate location. Thus to accomplish this insertion of an added enzyme requires skill and knowledge of a plant system, the proper transmembrane placement of the enzyme and lack of toxicity in the enzyme used.

Applicants believe that the above arguments and claim amendments overcome this rejection. Therefore, Applicants respectfully request that this rejection be removed and the claims allowed thereover.

Rejection Under 35 USC §112, Second Paragraph
Claims 1-7, 9-11 and 12

These comments are responsive to Items 9 and 10 of the Action.

In claim 1, the terms “having a human-type sugar chain” are defined on page 12, lines 7-22. Because Applicants invention is intended to encompass all such sugar chains made in a transformed plant, limiting this term would exclude intended glycoproteins. Further remarks for this breadth are provided in the next rejection section which we request is read also into this remarks section. Thus for any specific glycoprotein, the mammalian- or human-type sugar chain is either known or determined and comparison with that sugar chain made in the present transformed plants. It is known how to test to determine whether this feature has been met (for example hydrophilic interaction chromatography, and MALDI-TOF-MS). Applicants do not believe that any further limitation of this term is required and request that the Examiner reconsider this rejection.

The word “obtained” has been replaced with “produced” to comply with the Examiner’s suggestion. Proper antecedent basis by amendment for the terms “the gene of glycosyltransferase” and “the gene of an exogenous glycoprotein” has been entered into the above amended claim 1.

In claims 2 and 9, the terms “capable of conducting a transfer reaction of” has been defined from page 14, line 29 through page 15, line 15. Applicants would reasonably expect that any enzyme that is capable of performing the desired reaction *in situ* in the plant would cause the reaction to occur. In Applicants’ opinion the suggested wording is identical in result with that wording present in the original claim. However, to facilitate this Response, Applicants have entered the Examiner’s suggestion, but no limitation to either claim is intended thereby and no limitation of scope or equivalents is intended.

In claim 3, the above remarks for claim 1 with respect to “with a human-type sugar chain” also apply to this rejection.

In claims 7 and 12, it should be understood that a plant has the native enzymes so it can, and frequently does, add fucose and/or xylose to a sugar chain when the plant is adding sugar residues to its native protein or engineered glycoprotein. These claims specify that such addition of fucose and xylose is minimized. It is clear from page 12, lines 14-22, that the less of these plant sugars added the better in order to more closely simulate the mammalian-type sugar chain. The plant made human-type sugar chains may not be exactly identical to native human sugar chains (similarly for mammalian sugar chains), but the intent is to get the sugar chains to resemble the native (human or mammalian) as closely as possible. Diagrams (labeled “A” and “B”) are provided that illustrate these structural differences. Applicants believe that claims 7 and 12 are clear as presented and respectfully request that this objection be removed from both claims. The added wording “wherein the glycoprotein produced has no fucose or xylose linked to one or more of the core sugar chain, the outer sugar chain and the terminal sugar chain” results in a lowered fucose or xylose content as some fucose or xylose could be present in one of these chains, which result is supported by the wording in the specification, the data in the examples, Figure 20, and the Affidavits. Thus zero fucose or xylose is not required, but a reduction in their level occurs.

Claim 9 is amended as for claim 2 for the terms “capable of conducting a transfer reaction of” and for the same reasons as given above for claim 2. The word “enhance” has been amended above to read “improve the performance of” which is believed to be clearer in meaning.

In claim 10, GalT has been removed to clarify the intent of this claim.

Applicants believe that the above arguments and claim amendments overcome this rejection. Therefore, Applicants respectfully request that this rejection be removed and the claims allowed thereover.

Rejection Under 35 USC §112, First Paragraph
Claims 1-12

These comments are responsive to Items 11-13 of the Action.

In the present application Applicants have demonstrated the presence of galactose on N-linked glycan structures in transformed tobacco cells expressing human β -1,4-galactosyltransferase (hGalT) using Cauliflower mosaic virus (CaMV35S), with horseradish peroxidase (HRP) as the exogenous glycoprotein, and transformation with *Agrobacterium* (see Examples 1-3 in the specification). Using this teaching, a person skilled in the art could, without undue experimentation, perform a method of manufacturing a glycoprotein having a mammalian-type sugar chain, which method includes introducing a gene encoding a glycosyltransferase enzyme and a gene encoding an exogenous glycoprotein into a plant cell to produce a transformed plant cell and cultivating the transformed plant cell, as required by the amended claims.

Using the teaching in the specification as filed, the skilled person could also, without undue experimentation, produce a range of plant-produced glycoproteins comprising neither fucose nor xylose as required by some of the amended claims. In a similar manner, a skilled person, without undue experimentation, could produce a recombinant plant, or portion thereof, that produces mammalian-type glycoproteins.

The inventors have subsequently produced data for whole plants (tobacco and tomato plants) which shows similar results for N-linked glycan structures to that obtained for plant cells described in the present application. An Affidavit by the inventors is provided. These results demonstrate that glycosyltransferase, shown by galactosyltransferase and hGalT, when expressed in mature plants (present Affidavit) or calli (specification), modifies the structure of N-linked glycans in a manner similar to that seen in mammalian systems.

The Assignee and its affiliate have also performed additional experiments which establish the successful placement of galactose on N-linked glycan structures of human chorionic gonadotropin (HCG) in Whiskers®-transformed corn cells (corn calli) and regenerated transformed corn plants expressing hGalT and HCG, both of

which expressions were driven by the maize ubiquitin 1 promoter. These results are shown by an enclosed Affidavit by an employee of Assignee under whose supervision this work was performed.

Furthermore, a later published application (WO 01/29242) has shown that the scope of the present claims is reproducible. In this publication tobacco calli, soybean calli and corn calli were used to illustrate the successful placement of galactose on N-linked glycan structures of a human monoclonal antibody (hMAb) and collagen in biolistic-transformed calli using prolyl 4-hydroxylase (P4H) as the glycosyltransferase, which expressions were driven by the CaMV35S promoter, but no whole plants were used or regenerated. Thus Applicants invention has been confirmed by this later published application.

How to transfect tobacco plant cells with hGalT showing modified N-linked glycans was shown by Palacpac *et al.*, *Proceed. Nat'l Acad. Sci.* 96(8), 4692-4697 (13 April 1999). WO 01/31045A describes the expression of hGalT for indigenous glycoproteins in whole plants. Thus after the time of this invention, the art has shown that such transformations are possible and successful.

It is not critical that the sequences of the resulting plant produced glycoprotein be identical to that made in a human or mammalian system, but rather that the sequences are as close as possible so that the plant produced glycoprotein function the same as and preferably as well and efficiently as the human or mammalian produced glycoprotein. Thus the ultimate use made of the glycoprotein made by a transgenic plant system should be equivalent to that made by a mammalian system.

Thus Applicants have shown that the present method will produce the desired glycoprotein regardless of the plant stage (cells or whole plant), whether the plant is a monocot or dicot (lower plants such as moss and algae would also be anticipated to work), and with whatever exogenous glycoprotein is inserted to be glycosylated. With modification to the wording of the fucose and xylose claims above, Figure 20 does illustrate what is now claimed. Therefore, Applicants have shown that their invention was understood and possible and with teachings sufficient for it to be implemented.

Because the glycoprotein that is being made in plants would be known from another source (in order to be an exogenous glycoprotein) then the protein made by the plant can be compared for its sugar chain pattern with the known sugar chain pattern. Because the intent is to make a mammalian-type or human-type sugar chain on the plant prepared glycoprotein, the desired outcome can be determined. One way to make this determination is shown by an article by J. Zhang and D. I. C. Wang, *J. of Chromatography B*, 712, 73-82 (1998), copy provided, and another way is shown by the Affidavits. The structure attained may vary somewhat in sequence to attain that result because of expression in plants (for example, different codon optimization patterns, promoters, leader sequence). Thus the function of the present produced biomolecule is correlated to the function of the known biomolecule. The functional equivalence is what matters rather than the exact same structure.

There are well known classes of N-linked glycan enzymes for the claimed glycosylation method in plants (*i.e.*, glycosyltransferase) some of which are IUBMB Nos. EC 2.4.1.101, EC 2.4.1.143, and EC 2.4.1.144, which by their classification transfer mannose residues, and IUBMB No. EC 2.4.1.38, which by their classification transfer galactose. Thus all such enzymes do function for their intended use and are well known to one skilled in this art. Because the glycosyltransferase must be able to make a human-type or mammalian-type sugar chain glycoprotein, any enzyme that does not perform its usual function in this method in plants is excluded. Thus this invention is not a function to structure issue, but a function to function issue that is easily confirmed.

The citation by the Examiner to an article by Dinter *et al.* simply shows a well known fact that there are many native glycosyltransferase enzymes. Applicants have now shown by other published patents that other such enzymes are effective as exogenous glycosyltransferase enzymes (see WO 01/29242 discussed above).

With regard to the *Wands* [*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)] criteria raised in the Action: (1) whether or not undue experimentation would be necessary to practice this invention; (2) amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the

invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims.

In light of the work of others, as discussed above, since the priority date which shows that this invention can be applied, Applicants believe that points (1), (2), (4), (6), and (7) of *Wands* have been met. Points (3) and (8) of *Wands* are met by the instant teachings and Affidavits. Point (5) of *Wands* is raised in the following sections of this Action and the accompanying remarks to respond.

The use of the produced glycoprotein will be based on the selection of the protein to be glycosylated. Its use will already be known. The desired glycoprotein will have a known utility and been tested from a natural source or made in a microorganism or CHO cells. This is a new process to manufacture that glycoprotein and have the sugar chain added as close in structure to that already known to maintain the protein activity, folding, binding affinity, and other properties. Applicants believe that one skilled in the art will know how to achieve all the features of that product as now claimed.

Applicants believe that the above arguments, additional support by later publications and Affidavits and the above claim amendments overcome this rejection. Therefore, Applicants respectfully request that this rejection be removed and the claims allowed thereover.

Rejection Under 35 USC §102(e)

Claims 1-7

Anticipated by Umana *et al.*, US Patent 6,602,684 (filed 20 August 1999, issued 5 August 2003; priority to US Provisional 60/082,581, filed 20 April 1998)

These comments are responsive to Items 14 and 15 of the Action.

The cited patent discloses methods employing a host cell, GnT III, for antibodies (Fc regions required).

The importance of the desired sugar chain structure is discussed in the cited patent at column 1, lines 38-51. It specifically mentions that mammalian cells are the

preferred host cells (column 1, lines 52-53) and that plant cells, among other host systems, are least desired with the reasons why given (column 1, lines 56-61). Thus this cited patent teaches away from the present invention.

In the cited patent at column 12, lines 61-67, the use of a plant cell system is very briefly disclosed. To a person skilled in the art, this teaching is insufficient as to how to achieve the claimed result of the cited patent. It is not obvious how to determine what will work in a plant system. The enzyme must express in the plant, in the Golgi and in the correct location in the Golgi. Thus determining what promoters to use to get expression of the glycoprotein, in what organ of the plant, what is the leader sequence needed to attain this result, what is the method needed to detect the expression, and also the fact that some human transferases are toxic in a mammalian system (*e.g.*, hGnTIII in CHO cells were found to be toxic), makes it very difficult to use any mammalian information and apply it to a plant system. It is required that GalT attach to the Golgi in the proper position of the membrane to be effective. Thus if the GalT is in the wrong position in the Golgi it cannot function as the substrate it requires to act upon would not be present. (See Diagram C provided.) The teachings for a mammalian cell system do not even begin to address these issues. In fact one skilled in the art would be a different person in a mammalian system from a person skilled in the art for a plant system.

The only host system shown in the Figures of the cited patent is mammalian cells, preferably CHO cells. There is no teaching in the cited patent to enable any host cell system other than a mammalian system for such method. The cited patent states "any type of cultured cell line can be used" at column 9, lines 37-38 but proceeds to list only mammalian cell lines. The vectors given at column 12, line 42 through column 13, line 7 are for mammalian or yeast systems as host cells. There is no teaching how to use a plant cell, codon optimization method that is desired for a plant system is not mentioned or how to accomplish it, promoters for use in plants are not identified, growth conditions and separation, when desired, is not taught. Thus one skilled in these mammalian cells as a host system would not know how to make those modifications to obtain the present invention from the teachings of the cited patent. In addition the techniques used for plant cell transformation differ significantly from

those techniques used for mammalian and yeast system transformation. Therefore, how to obtain the desired result for transformation is not apparent or obvious.

The cited patent mentions at column 9, lines 12-36 that the host cell can have a variety of combinations of either an endogenous glycosyltransferase with an exogenous antibody or a fragment, or an exogenous glycosyl transferase with an exogenous antibody or fragment. In a plant system, however, the endogenous glycosyltransferase enzyme is not present, so that combination is not a possibility.

Because the host cell of the cited patent is only enabled for mammalian cell systems, and possibly yeast cell systems, the present invention directed to plant cells or whole plants is not disclosed or taught. Thus this cited patent is not relevant to the present claims.

Applicants believe that the above arguments and claim amendments overcome this rejection. Therefore, Applicants respectfully request that this rejection be removed and the claims allowed thereover.

Rejection Under 35 USC §103(a)

Claims 8-12 Anticipated by Umana *et al.*, US Patent 6,602,684 (filed 20 August 1999, issued 5 August 2003; priority to US Provisional 60/082,581, filed 20 April 1998), in view of Hein *et al.*, US Patent 5,959,177 (filed 3 May 1996, priority to 27 October 1989)

These comments are responsive to Items 16 and 17 of the Action.

The host cell systems are so divergent that the combination of these references appears to Applicants to be hindsight combination or an attempt at an obvious to try attempt rejection. As discussed above one skilled in the transgenic plant cell or transgenic whole plant art would not look to the mammalian art for guidance. These arts do not transfer the technology capabilities between them easily, if at all. The feature in common with these two cited patents is the antibody production desired. These methods of the two cited patents are divergent and would not be combined.

In fact the importance of the desired sugar chain structure is discussed in the cited Umana patent at column 1, lines 38-51. It specifically mentions that

mammalian cells are the preferred host cells (column 1, lines 52-53) and that plant cells, among other host systems, are least desired with the reasons why given (column 1, lines 56-61). Thus this Umana cited patent teaches away from the combination with the cited Hein patent and away from the present invention. None of the methods taught in any detail from the cited Umana can be used in the cited Hein patent.

The critical nature of the choice of the host cell line is discussed by N. Jenkins *et al.*, *Nature Biotech.* 14, 975-981 (August 1996), copy provided, where the differences in carbohydrate structures are described based on which expression system is selected, the culture conditions used, and the analysis employed for the carbohydrate structure. This article shows that shifting from one host cell system to another, even with all the technical differences that would have to be known and adjusted, still results in carbohydrate differences for both the pattern of sugars attached and in that different structures are formed on the glycoprotein. Thus the choice of a plant cell or whole plant system results in a different glycoprotein prepared from that of a mammalian cell system. Thus the glycoprotein made would be different from that obtained by the present claimed invention.

The cited Hein patent teaches that an antibody can be produced by a plant cell where the various antibody chains were introduced into different plant cells, the cells crossed (plant breeding) and then that transgenic plant grown and its progeny produce the antibody. This cited patent has no glycosylation of the antibody mentioned other than what the native plant might provide. Thus no attempt was done to make a mammalian-type or human-type sugar chain as required by the cited patent claims. Thus this cited Hein patent alone would not disclose the presently claimed invention or lead a person skilled in the plant art to try mammalian-type glycosylation.

Combining the teachings from the cited Umana patent with the cited Hein patent is just not technically feasible nor would the carbohydrate residue pattern obtained by either method be similar. This diverse carbohydrate pattern is accounted for by the way the carbohydrate is attached to the protein. To have a plant glycosylate a protein is a major modification of the plant's biosynthetic pathway. (See P. Lerouge *et al.*, *Plant Molecular Biology* 38, 31-48 (1998), copy provided.) Clearly, predicting how a carbohydrate pattern will result when a mammalian cell system is transferred to

a plant cell system is problematic at best. Also because the pathways for glycosylation are so different, the only recourse is to "try" to make it work. This is not a teaching that would enable one skilled in the plant art to implement the teachings from a mammalian cell system. Applicants contend that the combination of these references is technically unjustified.

Because the cited Umana patent also teaches that yeasts could be used, but without much guidance as to making that system function, the following article shows that changing from a human system to yeast results in significant glycosylation differences as well [S. R. Hamilton *et al.*, *Science* 301, 1244-1246 (29 August 2003); at Fig. 1, 1245, copy provided]. In an article by B. Choi *et al.*, *Proceed. Nat'l Acad. Sci.* 100(9), 5022-5027 (April 29, 2003), copy provided, the authors discusses the re-engineering of the glycosylation pathway for yeast to try to obtain a more human-type sugar chain for a glycoprotein made in yeast. Thus to obtain the desired result was not a simple insertion into yeast from a mammalian system as stated by the cited Umana patent. Clearly, the CHO system does not transfer to yeast easily. It is even a greater difference to apply a CHO system to plants.

Thus, until the present invention no one had managed to provide a way to obtain a human-type or mammalian-type sugar chain to be added to a protein by a plant where both the glycosyltransferase and the protein are exogenous to the plant. Additionally, to prevent the plant from attaching by its native mechanisms the fucose and xylose residues was not known in such a system.

Applicants believe that the above arguments and claim amendments overcome this rejection. Therefore, Applicants respectfully request that this rejection be removed and the claims allowed thereover.

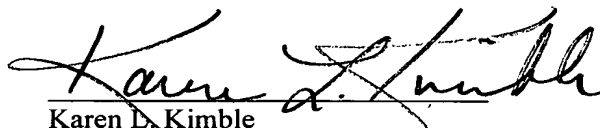
Items 18 and 19 of the Action do not require comments.

Conclusion

Applicants believe that in light of the above amended claims, Arguments and Remarks all claims as now amended are allowable over all the objections and rejections.

Reconsideration and allowance of the application are respectfully requested in view of the above. If there are any issues still outstanding after the Examiner's review of this Response, Applicants request that an interview either in person or by telephone be permitted at a mutually convenient time.

Respectfully submitted,



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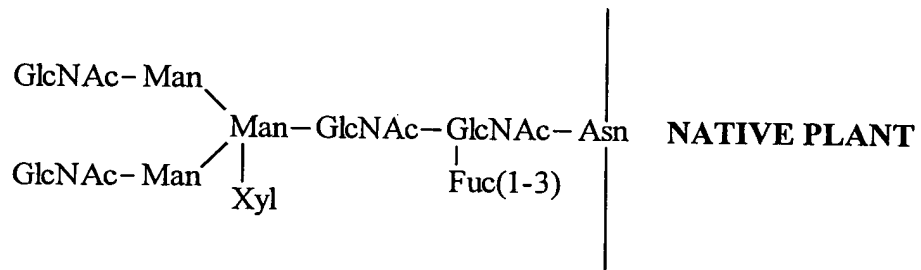
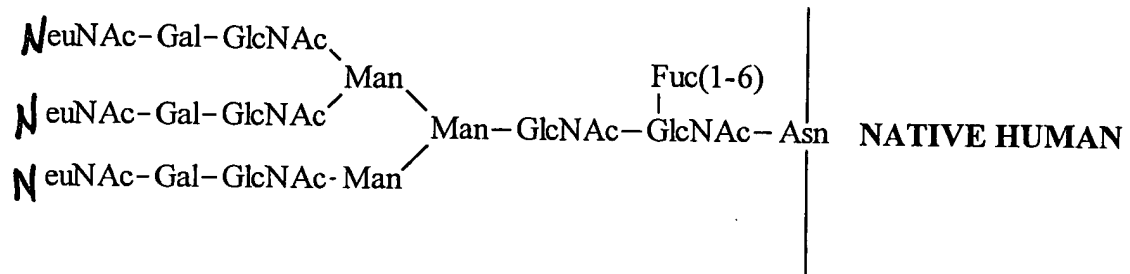
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Enclosures

Three (3) months extension of time – plus one copy
Affidavit by Inventors
Affidavit by Assignee employee
Copy of post card dated 10-08-03 for Inventorship Petition and copy of the Petition
IDS
Form 1449
Power of Attorney
Added Claims Fee Sheet – plus one copy
Diagrams – A, B and C
N. Jenkins *et al.*, *Nature Biotech.* 14, 975-981 (August 1996)
P. Lerouge *et al.*, *Plant Molecular Biology* 38, 31-48 (1998)
S. R. Hamilton *et al.*, *Science* 301, 1244-1246 (29 August 2003)
B. Choi *et al.*, *Proceed. Nat'l Acad. Sci.* 100(9), 5022-5027 (April 29, 2003)
J. Zhang and D. I. C. Wang, *J. of Chromatography B*, 712, 73-82 (1998)
Post Card for this Response

Diagram A

N-LINKED COMPLEX TYPE GLYCAN STRUCTURES



Glc NA_c = N-acetylglucosamine

Modifying Plant Glycan Structures

DOW

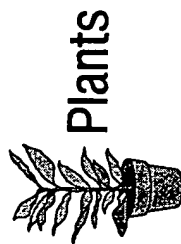
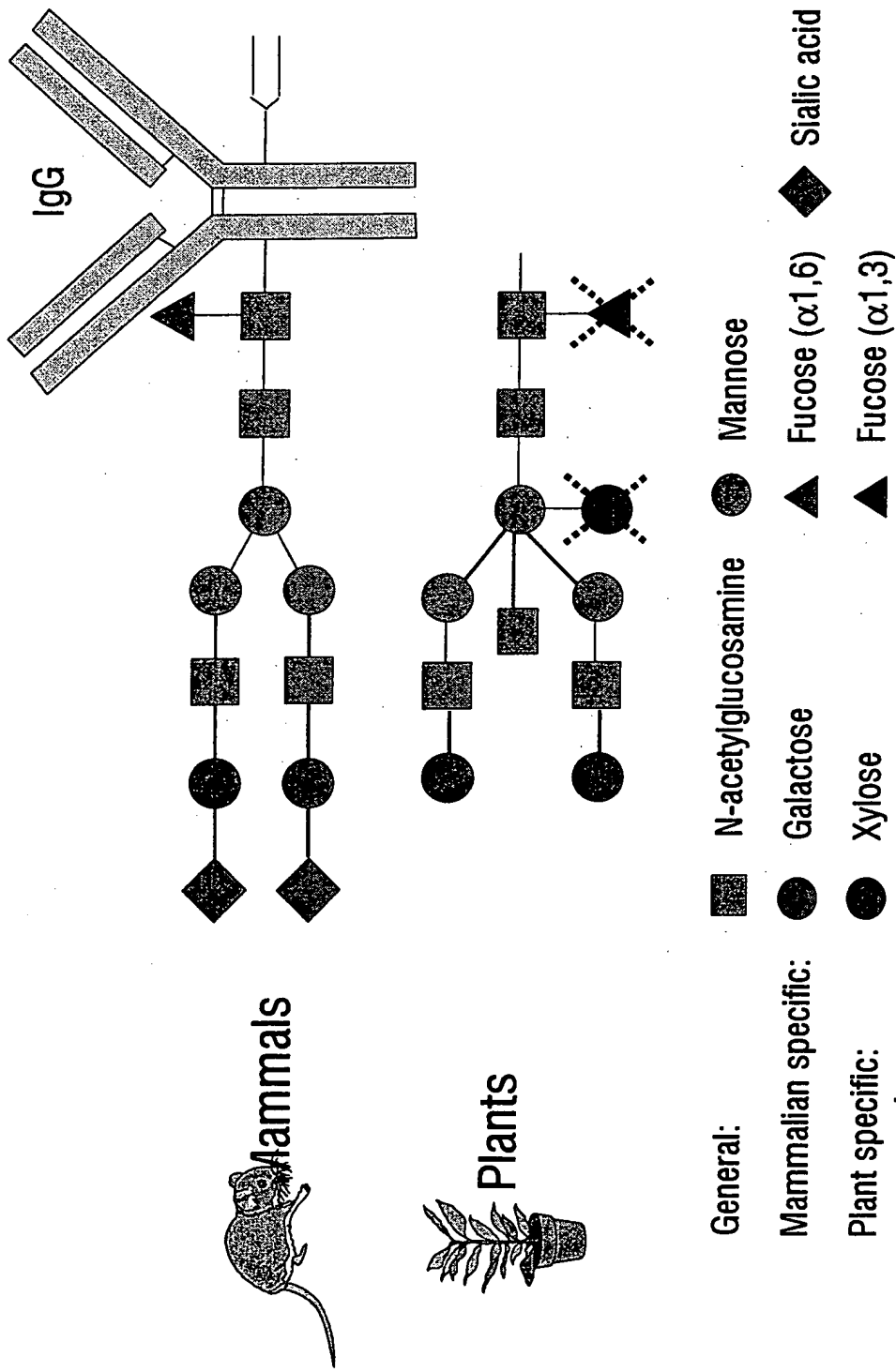


Diagram C

OVERALL SCHEMATIC FOR COMPLEX N-GLYCOSYLATION (Triantennary Complex Glycan Example)

